Donor Cell Leukemia Developing Six Years After Marrow Grafting for Acute Leukemia

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A patient who developed recurrent leukemia more than six years after marrow grafting from an HLA-identical same-sex sibling is reported. Difference in DNA restriction fragment length polymorphisms between donor and host demonstrated that the DNA in the recurrent leukemia sample was probably of donor origin. Possible mechanisms that could explain the long latent period between transplantation and expression of leukemic transformation are discussed. We conclude that future cases of late leukemic recurrence after marrow grafting should be studied to determine whether, in contrast to early relapses, late relapses occur in donor cells in most or all instances.

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DNA Restriction Fragment Length Analysis

Because there were no cytogenetic or other markers that could distinguish whether the malignant clone in the recurrent leukemia...
originated from cells of the marrow donor or represented reemergence of the patient's original leukemia, we exploited a restriction fragment length polymorphism that distinguishes the two genotypes. The clone pAW101, which originates from a highly polymorphous immunoglobulin heavy chain switch region was used in this analysis. High-molecular-weight DNA was prepared from the patient's normal skin fibroblasts, from the patient's marrow tumor cell sample, and from peripheral blood mononuclear cells of the donor. These were digested with EcoRI, electrophoresed on a 0.5% neutral agarose gel, transferred to nitrocellulose, and probed with the pAW101 probe as previously described.

RESULTS

Figure 1 shows that the analysis resulted in two bands of 19 and 16 kilobases (kb) when the patient's normal fibroblast DNA was used (lane A). However, DNA from both the tumor and marrow donor's mononuclear cells yielded bands of 16 and 12 kb (lanes B and C). The sensitivity of this analysis is such that we can estimate that at least 80% of the DNA in the tumor sample was of donor origin. The results of this analysis strongly suggest that all of the tumor DNA arose from donor cells, a conclusion that could best be supported by performing a similar analysis using different probes derived from different genomic fragments. Unfortunately, we lacked adequate amounts of DNA to repeat the analysis.

DISCUSSION

In 1976 this patient's leukemia was thought to be lymphocytic on the basis of morphological criteria. However, its failure to respond to treatment with vincristine and prednisone, commonly used for acute lymphocytic leukemia, and its subsequent response to daunomycin, cytosine arabinoside, and 6-thioguanine suggested that the disease may have been something other than acute lymphocytic leukemia at that time. Whatever the type of the original leukemia, the leukemia developing six years after transplant arose from a cell that was different from that of the original leukemia and probably arose in a donor cell.

Several possible mechanisms may exist, none of which can be proved at present, for the cellular or molecular events that led to this second malignancy. Previous occurrences of donor cell leukemia reported from this and other centers have all been observed within 36 months of transplantation. These early occurrences are compatible with relatively acute mechanisms of transformation. These mechanisms, which have been previously discussed, include transfer to the transplanted marrow cells of a dominant oncogene residing in the DNA of either an oncogenic virus or in chromosomes of degenerating irradiation-damaged host leukemic cells. In the present case, however, the six-year latent period between transplantation and expression of the leukemic transformation makes it more difficult to envision how such "single-hit" mechanisms might operate. A possible explanation for the long latent period may be found from recent studies in tissue culture and animal tumor systems. These studies suggest that in some cases more than one oncogene may be necessary for the full expression of neoplastic transformation. For example, this patient's leukemia may have resulted from transfer of one required oncogene at the time of transplantation and the activation of an additional required oncogene(s), which occurred after a long latent period.

These concepts are highly speculative and, of course, other factors may have contributed to expression of the leukemia. These factors include exposure of donor cells to methotrexate, impairment of immune surveillance of malignant clones by antithymocyte globulin and prednisone treatment, or chronic antigen stimulation of donor cells by minor histoincompatibilities with the host. The notion that these mechanisms played a role in inducing leukemia is perhaps less attractive because they are also operating in patients transplanted for aplastic anemia. We have successfully transplanted more than 200 aplastic anemia patients after conditioning with cyclophosphamide alone and methotrexate prophylaxis for acute GVHD and have not seen a case of leukemia developing in donor cells. Whatever the underlying mechanism, this case has significant implications for the interpretation of late relapses of leukemia in marrow graft recipients. The analysis suggests that the original leukemic cell population was eliminated by the transplantation procedure. It will be important to analyze additional cases in order to determine, in contrast to early relapse, whether most or all of late relapses occur in donor cells.
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