Development of Human T-Cell Lymphotropic Virus Type I–Associated Adult T-Cell Leukemia/Lymphoma During Immunosuppressive Treatment Following Renal Transplantation

Peter J. Jenks, Winsome Y. Barrett, Martin J. Raftery, Stephen M. Kelsey, Jon D. van der Walt, Sui P. Kon, and Judith Breuer

From the Departments of Virology, Renal Medicine, Haematology, and Histopathology, The Royal Hospitals NHS Trust, London, United Kingdom

Although it is recognized that there is an increased incidence of lymphoproliferative disorders among patients who have received immunosuppressive therapy following transplantation, there have been few reports of adult T-cell leukemia/lymphoma (ATLL) developing in previously asymptomatic carriers of human T-cell lymphotropic virus type I (HTLV-I) who have undergone transplantation. We describe the development of such a tumor in a man who was HTLV-I-positive and received immunosuppressive treatment following renal transplantation. As the number of individuals in ethnic groups at risk for organ transplantation increases, it would seem prudent to screen such individuals for carriage of HTLV-I before transplantation and to follow them prospectively to confirm if transplantation and immunosuppression predispose to the development of ATLL.

Adult T-cell leukemia/lymphoma (ATLL) was first described in Japan in 1977 [1] and was subsequently found to be etiologically associated with human T-cell lymphotropic virus type I (HTLV-I) [2]. HTLV-I is also endemic in the Caribbean [3]. Despite the increased risk of neoplasia complicating organ transplantation, to our knowledge, only two cases of ATLL developing in asymptomatic carriers of HTLV-I during immunosuppressive treatment following transplantation have been reported [4, 5]. We describe a patient in whom HTLV-I-associated ATLL developed during immunosuppressive treatment following renal transplantation.

In 1992 a 61-year-old man with end-stage renal failure secondary to IgA nephropathy underwent successful cadaveric renal transplantation; he received maintenance therapy with cyclosporine, azathioprine, and prednisolone. He was born in Grenada and had lived in the United Kingdom for 30 years. He was a widower and reported a single homosexual relationship 17 years ago. He had had numerous blood transfusions and had been treated for syphilis.

Nine months later he was admitted to the hospital because of a 2-week history of malaise, epigastric pain, and jaundice. Physical examination revealed lymphadenopathy and hepatosplenomegaly, and CT confirmed multiple lesions in the liver and pancreas and enlarged paraaortic lymph nodes. He had no lytic bone lesions or systemic or neurological symptoms. Laboratory values were as follows: hemoglobin, 15.3 g/dL; WBC count, 13.5×10^9/L; platelet count, 155×10^9/L; bilirubin, 101 μmol/L; alkaline phosphatase, 100 U/L; alanine aminotransferase, 156 U/L; γ-glutamyltransferase, 1,727 U/L; and calcium, 3.5 mmol/L. Microtiter particle agglutination (Fujirebio, Tokyo) retrospectively revealed that stored sera collected before transplantation was positive for HTLV-I and HTLV type II (HTLV-II), and the presence of HTLV-I was confirmed by the Retrovirus Reference Laboratory, Colindale, London. Acquisition of the virus could have occurred sexually or through infected blood transfusions. A retrospective review of four blood films demonstrated no abnormalities. Histologic examination of a lymph node biopsy specimen revealed a high-grade T cell lymphoma with features typical of ATLL: medium-to-large cells with markedly pleomorphic nuclei and a T cell population predominantly made up of CD4, CD3, and CD45RO cells. He was treated with a 5-day course of vincristine, doxorubicin, and cyclophosphamide; he appeared to tolerate this therapy well. However, 5 days after chemotherapy was stopped, he was found collapsed and could not be resuscitated.

For further investigation of the origin of the tumor, the biopsy sections were deparaffinized and digested with proteinase K. DNA was extracted, and HTLV-I and HTLV-II proviral DNA was detected by PCR analysis with oligonucleotide primers that amplify a 159-base pair fragment from the *tax* gene [6]. Samples were amplified with use of the following parameters: 40 cycles of denaturation at 94°C for 1 minute, annealing at 55°C for 1 minute, and extension at 72°C for 1 minute. The identification of the amplified product was confirmed by hybridization with the HTLV-I-specific oligonucleotide probe SK45 (results not shown) [6]. Multiplex PCR analysis with combined HTLV primers at a concentration of 15 μM and β-globin primers at a concentration of 0.125 μM demonstrated 159- and 268-base pair amplified products, respectively (conditions were the same as those described above).

Clonal integration of HTLV-I in the tumor cells can be demonstrated by Southern blotting of a fresh tissue sample,

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Reprints or correspondence: Dr. P. J. Jenks, Department of Virology, The Royal Hospitals NHS Trust, 37 Ashfield Street, London E1 1BB, United Kingdom.

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but this technique is not suitable for paraffin-embedded material. We used PCR analysis to confirm the presence of HTLV-I in the tumor cells. Incorporation of the β-globin and HTLV-I primers in the same reaction showed that there were approximately equal numbers of β-globin and HTLV-I genes in the tumor cells, but there was a much lower HTLV-I copy number in the patient's peripheral blood lymphocytes. This result suggests that sequences of HTLV-I DNA are present in tumor cells rather than in neighboring lymphocytes, thus suggesting that the tumor arose from a cell carrying HTLV-I and that the presence of HTLV-I is necessary to maintain the neoplastic phenotype.

The rapid progression to malignant disease in our patient may have resulted from the expansion of a preexisting lymphoma, although the fact that he was asymptomatic and the fact that review of films of his blood obtained before transplantation revealed no abnormalities would argue against this occurrence. Alternatively, immunosuppression and subsequent decreased T cell function could have led to reduced containment of proliferation of HTLV-I-infected polyclonal T cells, with eventual malignant transformation. This circumstance would be analogous to the development of Epstein-Barr virus–related lymphomas in transplant patients [7]. It is possible that the development of ATLL in this patient was a chance coincidence.

While the mechanism involved in increasing the risk of progression of asymptomatic HTLV-I carriage to ATLL remains unclear, our case and others suggest that transplant recipients may be at particular risk for this disorder. There are ~10,000 renal transplantations performed annually in the United States (Renal Association, United Kingdom Transplant Services, Bristol, United Kingdom), and since the estimated prevalence of HTLV-I carriage among asymptomatic blood donors is 0.025% [8], we estimate that two to three high-risk patients undergo transplantation each year. Although the exact prevalence of HTLV-I carriage among the transplant population is not known, it is likely that the cohort of long-term transplant recipients who are HTLV-I carriers is so far quite small because of the low rates of transplantation in Japan and the Caribbean. As more patients in at-risk groups are considered for transplantation, more cases of ATLL are likely to be seen, and in view of the poor prognosis associated with this condition, it would seem prudent to screen these individuals before operation. If an association between HTLV-I carriage and the subsequent development of posttransplantation ATLL is substantiated, it may be that those patients most at risk should be excluded from transplantation except in exceptional circumstances. A prospective analysis of the outcome of transplantation for such patients is now needed.

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