Lack of Correlation Between Human T-Lymphotropic Virus Type I DNA Integration and Clinical Course of Adult T-Cell Leukemia/Lymphoma

To the Editor:

Recently, Shimamoto et al. reported the existence of a correlation between the human T-lymphotropic virus type I (HTLV-I) DNA integration pattern and the clinical behavior of patients with adult T-cell leukemia/lymphoma (ATLL). They reported 3 of 89 ATLL patients with an abnormal HTLV-I DNA integration pattern on Southern blot examination, i.e., two bands after EcoRI digestion instead of only one band, as in most cases of ATLL. Interestingly, they correlated this abnormal integration pattern with a worse clinical course of the disease. At the initial stage of the disease, these 3 patients had pulmonary, gastric, and cutaneous involvement; they died within 8 months after diagnosis, compared with one third of the other patients (with only one band on Southern blot after EcoRI digestion) during the same period.

These findings should be viewed with caution. We recently reported the case of a dramatically indolent cutaneous lymphoma presenting ATLL with an extraordinary HTLV-I DNA integration pattern. Briefly, a 66-year-old French woman, with no known risk factor for a retroviral infection, presented at first examination in January 1990 with cutaneous plaques on the back and a tumor on the right thigh. Immunohistologic data were those of a cutaneous T-cell lymphoma of the mycosis fungoides type. Serum lactic dehydrogenase and calcium levels were normal. No extracutaneous involvement was detectable. HTLV-I DNA integration in cutaneous lesions and in peripheral blood lymphocytes showed an extraordinary pattern in that three bands after EcoRI digest was observed. To rule out the hypothesis of a partial DNA EcoRI digestion, the integration was studied on subsequent samples after DNA digestion with SacI, an enzyme that has no site in the HTLV-I provirus. The presence of three bands was again detected, thereby confirming the existence of three different integration sites (Fig 1). After NdeI digestion (NdeI has one restriction site at the two extremities of the HTLV-I proviral genome), only one band at 9 kb was detected, confirming that the virus was not defective.

Unlike the disease in the 3 cases reported by Shimamoto et al., the condition in our patient was extremely indolent. The lesions that appeared in January 1990 progressively extended to the whole body except the head (Fig 2). Between 1990 and November 1994, no extracutaneous involvement was detected with the usual staging procedures (bone marrow aspirations and computerized tomography scan) and no atypical circulating cells were detected on standard examinations. The Karnofski index remained greater than 70%. The polychemotherapies usually indicated in malignant T-cell proliferations were unsuccessful and hematologically were poorly tolerated. A trial with α-interferon associated with retrovir was stopped because of a neutropenia. Finally, cutaneous lesions dramatically responded to local and repeated radiotherapy.

The findings of our case contradict those of Shimamoto et al. We
believe that the existence of more than one HTLV-I integration site in the genomic DNA does not define a peculiar clinical profile of patients with ATLL and, therefore, cannot be taken into account when establishing prognosis. Further studies are needed to assess the clinical significance of the HTLV-I integration pattern in overt ATLL.

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Response

We have carefully considered the comments by D’Incan et al referring to our recent article on clinical implications of integration patterns of HTLV-I proviral DNA in ATL. Unlike the 3 cases we reported, their case had a normal level of serum lactate dehydrogenase, no atypical circulating tumor cells, no extracutaneous involvement, and indolent course, although the HTLV-I DNA integration in the cutaneous lesions and peripheral blood lymphocytes showed an unusual pattern in that three bands were observed after DNA digestion with EcoRI or Sac I, an enzyme that has no cleavage site in the provirus. Their case also had features similar to those seen in our cases, with two bands such as infiltrating skin lesions, which progressively extended to the whole body, and unsuccessful response to chemotherapy. However, some points require consideration in their case. (1) Detection of three bands of HTLV-I DNA both in cutaneous lesions and peripheral blood lymphocytes. We cannot understand why the three bands were detected in the peripheral blood lymphocytes, as well as in the cutaneous lesions, with no atypical circulating cells. In general, standard Southern blot analysis cannot detect monoclonal HTLV-I DNA integration without circulating tumor cells, as we previously showed in the lymphoma-type ATL. (2) Fresh or cultured tumor cells. Multiple copies of HTLV-I provirus have been reported to be detected in “cultured” leukemic cells, whereas only one copy was detected in the “fresh” cells. We always assayed fresh tumor cells in our cases and the condition was not described in their case. (3) Clonality of the cells. The clonality of the cells was confirmed in our cases by the detection of the T-cell receptor (TCR) gene rearrangement, but it was not mentioned in their case. Their detection of HTLV-I DNA was conducted with the restriction endonucleases, EcoRI, Sac I, and Nde I, without description of the HTLV-I probe used. We used the probe of an entire HTLV-I genome with EcoRI and Pst I. We recently have seen three new cases with unusual integration patterns. In the first case with two bands after EcoRI digestion, four clear bands containing viral-cellular DNA after Pst I digestion were detected in addition to the three internal fragments of 2.5, 1.8, and 1.2 kb. This 59-year-old Japanese woman showed severe hypoxemia and lung involvement at presentation, similar to our previous report. The TCR-β gene rearrangement was confirmed. The second patient was a 51-year-old Japanese man found by chance to be positive for the HTLV-I antibody at examination for blood donation. He had no symptoms and a normal leukocyte count with a few (5% to 10%) atypical lymphocytes. EcoRI digestion showed two bands and Pst I digestion showed only three internal fragments without clear bands containing viral-cellular DNA. The TCR gene rearrangement was not found. This was considered to be a polyclonally HTLV-I DNA integrated case and the existence of some HTLV-I–infected oligoclones was suggested. Therefore, the detection of three bands after EcoRI or Sac I digestion and one band after Nde I digestion in their case is not considered to be sufficient to demonstrate the clonality of the cells. The third case had two different tumor clones in a single patient simultaneously, which was distinguishable by the HTLV-I integration and the TCR-β gene rearrangement patterns. His clinical features were described elsewhere in detail. Such a case with the different clones has also been suggested by another Japanese group. D’Incan et al did not mention the possibility of multiclones in their case. (4) Immunologic data. They described that the immunologic data were those of a cutaneous T-cell lymphoma of the mycosis fungoides type. This might mean that the CD25 antigen (interleukin-2 receptor) was not expressed on the tumor cells, unlike as in our cases. Because the diminished expression of CD25 may explain in part the more indolent course, the immunologic data should be compared in patients in endemic and nonendemic areas. Moreover, parochial differences of HTLV-I variants such as HTLV-Ib and Pst I or Sac I type6 have been reported and might explain the differences in the clinical features between the French and Japanese cases.

Our speculation is that the integration site of the HTLV-I provirus into the host cell DNA might have implications for heterogeneity in the clinical manifestations of this disease. When multiple sites are integrated with the HTLV-I provirus, the risk for acquiring clinical aggressiveness may increase with the number of integrations. We believe that such studies may provide us with interesting information concerning the relationship between the virus integration and the clinical manifestations. Also, the data may be helpful for us in better understanding the mechanism of the development of ATL if studies are performed carefully. However, as suggested in D’Incan et al’s letter, further precise and extensive studies would be needed to assess the correlation between the clinical features and the HTLV-I provirus integrations.
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