Deleted HTLV Retrovirus May Be Involved in the Development of Cutaneous T-Cell Lymphomas

To the Editor:

In an interesting recent article, Lisby *et al* [1] reported the absence of HTLV-I (human T lymphotropic virus type I) or HTLV-I–related provirus in DNA of skin lesions of 21 patients with a cutaneous T-cell lymphoma (CTCL) and seronegative for HTLV-I. They used the very sensitive polymerase chain reaction technique (PCR), with 10 primer pairs that amplify the conserved sequences between HTLV-I and HTLV-II, and span the *pol* (between nucleotides 2693 and 3345), *env* (between nucleotides 6157 and 6496), and *tax/LTR* (between nucleotides 7480 and 8659) genes. Their conclusions were as follows: 1) as sensitive as the PCR procedure is, there is no HTLV-I–related genome in the skin specimens of CTCL; 2) the putative virus associated with CTCL is distantly related to HTLV-I and thus, the HTLV-I–specific primers did not amplify it, even in low-stringency conditions of annealing; and 3) the infection by HTLV-I was processed on the "hit and run" mode, in which the virus disappeared during the evolution of the disease.

We agree totally with these conclusions but we wish to suggest a fourth possibility, which is the infection by a largely deleted HTLV-I provirus. Indeed, deleted retroviruses are known to be associated with some leukemic processes in animals (e.g., FTLV in feline leukemias [2]) and in humans (HTLV-I in some cases of adult T-cell lymphoma [3]). During the period when the article of Lisby *et al* was submitted, Hall *et al* [4] reported the case of an American patient with mycosis fungoides who was seronegative for HTLV-I, and from whom a B-cell line was established and found to be infected by a largely deleted HTLV-I provirus. This deletion spanned the entire *pol* gene and parts of the *gag* and *env* genes. Moreover, using PCR, these authors found the HTLV-I provirus with variable deletions in cutaneous lesions of five additional patients with CTCL. In addition, using PCR, we have looked recently for the association between HTLV-I and CTCL in a series of 51 patients with CTCL who were seronegative for HTLV-I [5] in a nonendemic area for HTLV-I in France. We detected a HTLV-I provirus deleted in the *pol* region in the peripheral lymphocytes of a woman with mycosis fungoides. In accord with Hall *et al*, we think that it cannot be excluded that deleted retrovirus may play a role in the pathogenesis of CTCL, and that, as these deletions seem to be variable from patient to patient, this could be an explanation for the negative results of the PCR search. Moreover, a large deletion in the *pol* gene would explain a low (or absent) production of viral antigenic proteins and the seronegativity for HTLV-I of patients with CTCL [4]. Finally, in nonendemic areas the incidence of HTLV infection in CTCL is probably low, because the virus was detected in only one of 51 cases in our series.

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REPLY

We are pleased that D'Incan *et al* agree with our conclusions [1]. We wish, however, to emphasize that the second and third "conclusion" cited by D'Incan *et al* were hypothetical discussions put forward by us and *not* conclusions based upon our experiments [1].

The possibility put forward by D'Incan *et al*, that a largely deleted HTLV-I provirus is involved in the pathogenesis of CTCL, is not supported by the experiments described in our article. Our 10 primer sets detect conserved HTLV-I/II proviral sequences from position 1703 to position 8659 (10 fragments within the 6957 bases) in the prototype HTLV-I genome, and a deletion thus has to be even larger to be "overlooked" in our setup, or, less likely, consist of several deletions covering all our target regions. The 5.5-kilobase deleted HTLV-I provirus reported by Hall *et al* [2] would have been detected by our two tax/LTR primer sets, and is not present in our patient group. We do not agree with the suggestions by D'Incan *et al* that the negative results by polymerase chain reaction could be explained by variation from patient to patient in the deletions affecting the putative integrated HTLV-I provirus. We find it very unlikely that all of our patients should have deletions covering all 10 target sequences. Although we wish to emphasize that our findings do not support a role for HTLV-I/II or an HTLV-I/II–related virus in patients with CTCL, we agree with D'Incan *et al* that such a virus could be present in a small subset of CTCL patients. However, because D'Incan *et al* found a deleted HTLV-I provirus in one of 51 patients with CTCL, and we did not find HTLV-I/II or an HTLV-I/II–related provirus in any of 21 patients with CTCL, it is unlikely that such a virus could play a major role in the pathogenesis of CTCL, at least in the two patient populations described here.

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