A Case of Adult T-cell Leukemia/Lymphoma with an Indolent Clinical Course has an Unusual Proviral DNA Integration Pattern

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Sir,

Adult T-cell leukemia/lymphoma (ATL) is a peripheral T-cell malignancy caused by human T-cell lymphotrophic virus type I (HTLV-I). The characteristic clinical features of ATL include generalized lymphadenopathy, leukemic cells of T-cell origin with highly convoluted nuclei, skin involvement, hypercalcemia and rapid progress of the clinical course. Relatively high rates of HTLV-I infection are observed in parts of Japan, the Caribbean, South America and Africa (1). The transmission of HTLV-I is mainly from mother to child through breast-feeding (2). The subsequent integration of the HTLV-I provirus into T cells is thought to be a random event that occurs during the carrier state. Polyclonal integration patterns of HTLV-I proviral DNA have been demonstrated by Southern blot analysis as the so-called smear pattern in asymptomatic HTLV-I carriers. Of these randomly infected cells, a cell clone is thought to be selected for preferential growth. Although the mechanism of clonal selection remains unclear, the HTLV-I proviral DNA integration pattern can progress from undetectable to polyclonal, or to monoclonal (1). Recently, we encountered a patient with ATL with an indolent clinical course.

CASE REPORT

A 59-year-old man was first seen in our hospital in February 2001 for the evaluation of skin eruptions. He first noticed reddish papules on his right medial canthus and the dorsum of his right hand when he was 24 years old. Similar eruptions appeared around both nostrils and on both ears at the age of 35. Those eruptions slowly enlarged and increased. On physical examination, reddish papules and nodules were noted around both eyes, around both nostrils (Fig. 1), on both ears and on the dorsum of his right hand. The peripheral blood counts revealed a leucocyte count of 5.7×10^9/l without any atypical lymphocyte. However, the anti-HTLV-I antibody was positive. Lactate dehydrogenase was 173 IU/l and serum calcium was 9.5 mEq/l. No abnormalities were found by bone marrow examination, computerized tomography or gallium scintigram. No lymphadenopathy was noted. Biopsies of the nodules around the nostril and on the right hand revealed dense diffuse infiltrates of pleomorphic neoplastic cells in the dermis, with small foci in the epidermis. Southern blot analyses for HTLV-I integration and T-cell receptor-β gene in the biopsied sample from the nostril showed several bands with different intensities (Fig. 2). We diagnosed this patient as a smouldering type of ATL with skin manifestations. The nodule on his right hand was surgically removed and the remaining nodules on the face were treated with an electron beam (total 50 Gy). There was no sign of recurrence one year after treatment.

Fig. 1. The nostril lesion showing papules and nodules.

DISCUSSION

The most characteristic feature of our patient is a very indolent clinical course of 35 years and a multiple integration pattern of HTLV-I, as judged by Southern blot analysis. Multiple HTLV-I integration patterns have been reported to occur in up to 20% of ATL patients studied (3–5). Multiple integration patterns can be demonstrated as multiple bands of the same or different intensity. Multiple bands of the same intensity are considered to indicate a single tumor cell clone that has multiple copies of the HTLV-I provirus. Whereas, multiple bands of different intensity, as were shown in our patient, are considered to indicate multiple tumor cell clones, each of which has one copy of the provirus (4). The clinical features of patients with multiple integration patterns have been compared with those of patients with an ordinary single HTLV-I provirus integration (6, 7). To date, patients with multiple bands of the same intensity are believed to have an extremely aggressive clinical course, while patients with multiple bands of different intensity tend to have an indolent course (3, 4). The clinical features of ATL patients with multiple integrations of HTLV-1 proviral DNA from

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Table I. *Clinical features of patients with adult T-cell leukemia with multiple integrations of HTLV-I proviral DNA.*

Patient	Age/Sex	Clinical subtype[a]	Organ involvement	Intensity of multiple bands	Suggested no. of tumor cell clones	Survival[b] (months)	References
1	75/F	Acute	LN, PB, pleura	Same	One	4	6, 9
2	69/F	Acute pleura, muscle	LN, PB, skin, stomach	Same	One	6	6, 9
3	42/M	Acute	LN, PB, lung, retina	Same	One	8	6, 9
4	55/M	Chronic	LN, PB, skin	Different	Two	+25	9
5	48/M	Smouldering	LN, PB	Different	Three	+51	9
6	57/F	Acute	LN, PB, skin	Different	Two	19	9
7	51/M	Smouldering	PB	Different	Two	+86	3
8	24/F	Chronic	PB, skin	Different	Two	+75	8
9	77/F	Smouldering skin		Different	Three	+48	7
10	73/F	Chronic	LN, PB, skin	Different	Four	+18	5
11	59/M	Smouldering skin		Different	Five	+18 (300?)	Present case

[a]The clinical subtype proposed by the Japanese Lymphoma Study Group. [b]+: still alive when reported.
LN: lymph node; PB: peripheral blood.

published reports are summarized in Table I. Our patient had ATL skin manifestations for 35 years without any sign of other organ involvement. Although the overall outcome of ATL may depend on multiple risk factors such as the expression of CD25 antigen of the malignant cells (7), the indolent clinical course of our patient can be related to multiple tumor cell clones, which were suggested by the HTLV-I integration pattern.

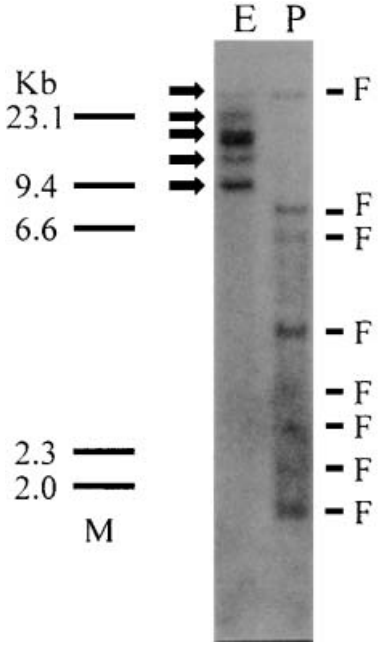

Fig. 2. Southern blot analysis for humanT-lymphotrophic virus type I integration using EcoRI or PstI endonuclease. Five bands of apparently different intensity are shown after EcoRI digestion from the skin manifestation *(arrows)*. M: molecular weight standards; E: EcoRI; P: PstI; F: flanking bands.

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