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LETTERS TO THE EDITOR

Lesional mRNA Expression of Th1 Cytokines in Adult T-cell Leukemia/Lymphoma

Sir,

Adult T-cell leukemia/lymphoma (ATL) represents a malignant proliferation of mature $CD4^+$ T-cells. ATL occurs in patients infected with the retrovirus HTLV-1 and is characterized by a variety of cutaneous lesions, including tumors, multiple papules and erythroderma. The clinicopathological features of ATL cutaneous lesions are diverse and may occasionally be indistinguishable from various forms of cutaneous T-cell lymphoma (CTCL), which usually show the same phenotype ($CD4^+$, $CD8^-$) as ATL (1, 2). In such circumstances, the diagnosis of ATL must be confirmed by positive serology and the detection of a monoclonal integration of HTLV-1 proviral DNA into the tumor cells.

It has been postulated that cytokines released from neoplastic or reactive cells may lead to the characteristic histogenesis and clinical features found in malignant lymphomas (3). The clinical and histologic alterations in patients with ATL may be attributed, at least in part, to abnormal cytokine secretion either by neoplastic T-cells or by accompanying reactive T-cells. Recently, Th2 cytokine mRNA expression in skin lesions in CTCL was shown by using RT-PCR amplification (4). Although phenotypically similar ($CD4^+$, $CD8^-$), the differences observed in the clinical course between CTCL and ATL patients suggest that distinctive cytokine patterns may exist among them. In the present study, we examined the local mRNA expression of cytokines in skin lesions from ATL patients to determine which cytokines are potential mediators in ATL.

Two patients with ATL (smouldering type) were studied. A diagnosis of ATL was established by demonstrating the monoclonal integration of HTLV-1 proviral DNA into the tumor cells and the presence of HTLV-1 antibody in the serum. Total RNA was extracted from skin biopsy specimens, and the cytokine mRNA expression was then measured by an RT-PCR assay, while the PCR products were transferred to nylon membranes and then hybridized to an internal ^{32}P-labeled probe, as reported previously (5). In skin lesions from the ATL patients, both IFN-γ and IL-2 mRNA were detected. However, neither IL-4 nor IL-5 mRNA was detected in any of the ATL patients (Fig. 1).

Using RT-PCR amplification, we demonstrated the presence of mRNA for IL-2 and IFN-γ, but no evidence of mRNA for IL-4 or IL-5 was observed in the skin lesions of the ATL patients, suggesting that the malignant T-cells of ATL are of a Th1 subtype based on the expression of the Th1 cytokines. This finding contrasted with that for the skin lesions of CTCL patients, which demonstrated a Th2 cytokine message (4). The malignant T-cells of ATL may thus elaborate a different set of cytokines than those of CTCL. These observations support the concept that ATL is a disease distinct from CTCL.

However, our data did not provide any direct evidence that the malignant T-cells of ATL are the source of Th1 cytokine mRNA. Other cutaneous cellular sources, such as accompanying reactive T-cells, could not be ruled out, based on our study. Recently, T-cell clones of the Sézary syndrome, a leukemic variant of CTCL, have been reported to display Th2 cytokines (6). In contrast, some ATL cell lines, established from peripheral blood lymphocytes of ATL patients, have been found to express IFN-γ mRNA and a low level of IFN-γ not associated with IL-4 or IL-4 mRNA production (7). These observations support the possibility that Th1 cytokine mRNA in skin lesions from ATL may be derived from the malignant T-cells of ATL. Further in situ hybridization studies are expected to clarify the precise localization of Th1 cytokine mRNA.

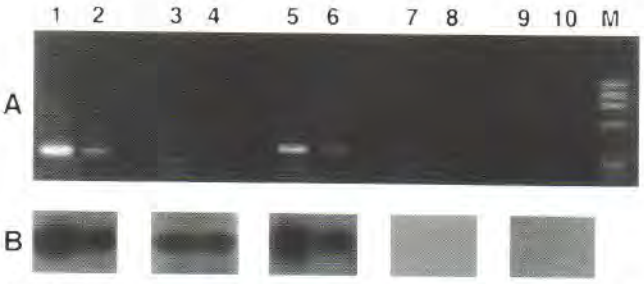

Fig. 1. The cytokine profiles of skin lesions from two ATL patients. A: An ATL skin lesion was examined for its cytokine mRNA expression by using an RT-PCR assay. The total RNA extracted from each biopsy specimen was reversely transcribed into cDNA and then amplified by PCR with primers specific for CD3δ (*lanes 1, 2*), IL-2 (*lanes 3, 4*), IFN-γ (*lanes 5, 6*), IL-4 (*lanes 7, 8*), and IL-5 (*lanes 9, 10*). The predicted sizes of the PCR products were 316, 266, 356, 317 and 405bp, respectively. The DNA size markers (M: φ-X174/Hae III digest) are shown in the last lane on the right in the panel. *Lanes 1, 3, 5, 7* and *9*; one patient. *Lanes 2, 4, 6, 8* and *10*; the other patient. B: Hybridization of PCR products. The PCR products for CD3δ, IL-2, IFN-γ, IL-4, and IL-5 cDNA were transferred to nylon membranes and then hybridized to an internal ^{32}P-labeled probe.

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