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 32P-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

Fig. 1. The cytokine profiles of skin lesions from two ATL patients.

A: An ATL skin biopsy 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 CD36 (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 455 bp, 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, 2, 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 CD36, IL-2, IFN-γ, IL-4, and IL-5 cDNA were transferred to nylon membranes and then hybridized to an internal 32P-labeled probe.

study. Recently, T-cell clones of the Sézary syndrome, a leukemia 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.

REFERENCES


Anti-230 kDa Circulating IgE in Bullous Pemphigoid: Relationship with Disease Activity

Sir,

Patients with bullous pemphigoid (BP) may have circulating IgE (1), in addition to IgG directed at hemidesmosomal proteins of 230 and 180 kDa. Such IgE have been found to be associated with the disease activity and, occasionally, to herald its exacerbation (2). More recently, they have been shown to bind the 230 kDa antigen (3).

Lately, a BP recombinant protein of 55 kDa (rBP55) has been generated from a cDNA sequence which encodes for the carboxyterminal region of the 230 kDa BP Ag (4). Such protein has been shown to be highly immunogenic and antigenic, providing a highly specific target for antibodies circulating in BP patients.

In the patients we describe, rBP55 contributed to the understanding of the relationship of circulating IgE with the disease activity.

We studied two male patients (BL and RG), 67 and 59 years old, with BP. The diagnosis was made on the basis of clinical examination, histology and direct immunofluorescence. Both patients were studied by indirect immunofluorescence (IF) on monkey esophagus as substrate and serum levels of total IgE serum (RIA). In addition, the serum level of IgG and IgE directed to the rBP55 protein was studied by Western blot, using anti-human polyclonal IgG and monocalonal IgE.

BL was followed up from 1989 to 1995 and RG from 1993 to 1995. BL was treated with 1 mg/kg/day prednisone from 1989 to 1990 and with prednisone and azathioprine in 1992. Because of iatrogenic diabetes and peptic ulcer, BL was given cyclosporin A (CyA) (5 mg/kg/day) from 1994 to 1995. RG was treated from 1993 to 1995 with CyA (5 mg/kg/day) because of diabetes.

The onset of BP in our cases was marked by high serum levels of non-specific IgE and basal membrane zone (BMZ)-bound IgG. When challenged with the rBP55 protein, specific IgG and IgE were found. Only anti-rBP55 IgE were somehow related to the disease activity, while anti-rBP55 IgG were not. The latter remained positive (over a 6-year follow-up in BL), even when anti-BMZ IgG detected by IF were absent (RG) (Table 1). In our cases, therefore, anti-rBP55 antibodies, especially IgE, proved to be more specific than anti-BMZ antibodies.

After the introduction of CyA a marked rise of total IgE was observed, fuelling doubts as to its role in BP pathogenesis. In fact, CyA has been shown to up-regulate the IgE response at low doses such as those used in our cases, while high doses have an inhibitory effect (6). In BP, however, such up-regulation may apply only to non-specific IgE, masking the behaviour of the ones directed at the 230 kDa antigen, which in our cases were related to the disease activity.

In conclusion, we have confirmed that, at least in some BP patients, the titres of the anti-BMZ IgG have no significant relationship with the disease activity. Instead, the serum levels of specific IgE directed at the 230 kDa antigen may often be a guide for treatment, if confounding factors, such as CyA, are not introduced.

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