ELEVATED LEVELS OF cICAM-1 IN PATIENTS WITH HUMAN T-CELL LEUKEMIA VIRUS TYPE I ASSOCIATED MYELOPATHY AND ADULT T-CELL LEUKEMIA

To the Editor:

Infection with human T-cell leukemia virus type I (HTLV-I) is etiologically associated with adult T-cell leukemia (ATL) and HTLV-I-associated myelopathy (HAM). While ATL is a rapidly progressive malignancy associated with morphologically abnormal circulating T cells, hypercalcemia and splenomegaly, HAM is characterized by focal T-cell infiltrates in the central nervous systems and a hyperimmune-state involving both cellular and humoral immune systems. In the mechanisms by which HTLV-I causes both T-cell leukemia as well as an inflammatory neurologic disorder are not well understood, but are thought to be related to T-cell activation by the virus. Indeed, HTLV-I has recently been shown to induce proliferation of resting T lymphocytes by cognate interactions involving the CD2/LFA-3 and LFA-1/ICAM pathways.

ICAM-1 (CD54) is a cell surface glycoprotein expressed on many cell lineages and functions in intercellular adhesion by binding to its ligand, LFA-1 (CD11a/CD18), a heterodimeric complex that is a member of the leukocyte integrin family. The cell surface expression of ICAM-1 is augmented both by cell activation and by certain inflammatory cytokines, such as interleukin-1 (IL-1) and interferon-γ (IFN-γ). Recently, a circulating form of soluble ICAM-1 (cICAM-1) has been identified, which can bind specifically to LFA-1 cell surface. cICAM-1 is believed to be released as an indirect consequence of inflammation or tissue damage in certain inflammatory diseases, including asthma, rheumatoid arthritis, and malignant melanoma.

To analyze the role of cICAM-1 in HTLV-associated disease pathogenesis, sera from HAM (n = 21) and ATL (n = 13) patients, from HTLV-I–positive asymptomatic carriers (n = 22) (all were confirmed to be HTLV-I by using type-specific oligoprobes and oligopeptides), and from HTLV seronegative individuals (n = 19) were assayed for cICAM-1 in an enzyme immunoassay. Briefly, immobilized monoclonal antibody (CL203) directed against the domain 4 of ICAM-1 was used as a capture antibody and biotinylated monoclonal antibody (R6.5) directed against domain 2 of ICAM-1 was used as detecting antibody. All specimens were run in duplicate and read against a standard curve generated with purified soluble ICAM-1 (8 to 1,024 ng/mL) (Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT).

Levels of cICAM-1 (Fig 1) were significantly increased both in patients with HAM (342 ± 148 ng/mL) and in those with ATL (360 ± 178 ng/mL) when compared with either normal controls (157 ± 61 ng/mL; P < .001 for both comparisons) or with asymptomatic HTLV-I carriers (215 ± 124 ng/mL; P < .01 for both comparison); levels of cICAM-1 in asymptomatic HTLV-I were within the range for normal controls. Despite the higher levels of cICAM-1 in the serum from patients with HAM, no significant difference in the cell surface expression of ICAM-1 (CD54) were observed by flow cytometric analysis as compared with asymptomatic HTLV-I carriers and the normal controls (data not shown).

While the functional characteristics of cICAM-1 are not well defined, it could act to promote transmembrane signalling to the lymphocytes by binding to the family of leukocyte adhesion molecules and eventually resulting in T-cell activation. Alternatively, cICAM-1 could compete with membrane ICAM-1 on the endothelial cell, thus regulating cell adhesion. It is pertinent to add that increased T-cell–endothelial cell adherence has been reported in patients with HAM, and increased cICAM-1 observed in the serum of these patients may either represent a proteolytic cleaved membrane ICAM-1 from the endothelial cells or may represent an alternatively spliced form of ICAM-1 mRNA. Alternatively, the transcriptional regulation of the ICAM-1 by the transactivating protein (tax) of HTLV-I may in part be responsible for the increased levels of cICAM-1 in patients with ATL and HAM. Indeed, the promoter region of ICAM-1 contains putative binding sites for several transcription factors, including NF-κB, AP-1, and SP-1. It is conceivable that tax might transactivate ICAM-1 promoter through one of these transcriptional factors.

Thus, the elevated levels of cICAM-1 in serum of patients with HAM, together with recent findings demonstrating inhibition of spontaneous T-cell proliferation in patients with HAM with anti–ICAM-1 antibodies suggests a pathogenic role for ICAM-1 in this disorder. The significance of increased cICAM-1 in ATL is not
clear at this time; it is conceivable that cICAM-1 in these patients might be a consequence of T-cell activation, tissue destruction, or nonspecific proteolysis. Further studies are needed to determine the physiologic role of cICAM-1 in the pathogenesis of either disease and whether blocking of the leukocyte adhesion might provide an effective therapeutic approach to anti-inflammatory reaction observed in patients with HAM.

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REFERENCES
Elevated levels of cICAM-1 in patients with human T-cell leukemia virus type I associated myelopathy and adult T-cell leukemia [letter]

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