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*Review*

# Pathological mechanisms of human T-cell lymphotropic virus type I–associated myelopathy (HAM/TSP)

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**The recent studies have greatly improved our understanding of the pathological mechanisms of human T cell lymphotropic virus type I (HTLV-I)-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The pathological mechanisms of HAM/TSP based on the histopathological, immunological, and molecular analysis with emphasis on the longitudinal alterations of the disease will be discussed. Immunohistological examination revealed the existence and the activation both of HTLV-I-infected $CD4_+$ cells and HTLV-I-specific $CD8_+$ cytotoxic T lymphocytes in the spinal cord lesions, which suggest that they play an important role in the pathogenesis. Increased expression of several cytokines, Fas/Fas ligand, adhesion molecules, and molecules influencing T cell migration in the lesions have been reported. These cell infiltrates and cytokines they secrete in the lesions may damage bystander neural tissue. Furthermore, longitudinal alterations in the affected spinal cords suggest that the inflammatory process is gradually decreased. Epidemiological studies show that less than 5% of infected individuals develop HAM/TSP and indicate that increased proviral load of HTLV-I is a strong predictor for the development of HAM/TSP. A recent study has shown that the autoantibody for the ribonuclear protein-A1 can cross-react with HTLV-I Tax protein and inhibit neuronal firing ex vivo, indicating that a molecular mimicry of the humoral immune response may be involved in the pathogenesis of HAM/TSP. Based on these studies, two hypotheses can be proposed for the pathogenesis of HAM/TSP, where cellular and humoral immune responses both play important roles.** *Journal of NeuroVirology* (2002) **8,** 359–364.

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## Introduction

Human T-cell lymphotropic virus type I (HTLV-I) is known as the causative agent for adult T-cell leukemia (ATL). This same virus was found to be related to another human disease, a progressive spastic paraparesis, found independently in two areas of the world, the Caribbean basin and Japan. In the Caribbean basin, 59% of patients with tropical spastic paraparesis (TSP) had antibodies to HTLV-I (Gessain *et al*, 1985). In Japan, a high prevalence of primary lateral sclerosis or spinal spastic paraparesis was found in South Kyushu (Osame *et al*, 1975). A follow-up study of this disorder established the existence of a new disease associated with HTLV-I, named HTLV-I–associated myelopathy (HAM) (Osame *et al*, 1986, 1987; Osame and Igata, 1989). The disease is now known by the acronym HAM/TSP (World Health Organization, 1989; Osame, 1990). The clinical and laboratory guidelines for the diagnosis of HAM/TSP have also been formulated, based on the recommendation of the World Health Organization meeting (World Health Organization, 1989; Osame, 1990).

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HTLV-I is estimated to infect approximately 10 million people worldwide. There are large endemic areas in southern Japan, Central and West Africa, the Caribbean, Central and South America, the Middle East, and smaller foci in the aboriginal populations of Australia, Papua New Guinea, and northern Japan. In Europe and North America, the virus is found chiefly in immigrants from these endemic areas and in some communities of intravenous drug users. Within the endemic areas, the seroprevalence varies between 1% and 20%. In contrast to the human immunodeficiency virus (HIV), HTLV-I causes diseases in only about 5% of infected people. The number of patients with ATL and HAM/TSP is estimated to be more than 3000 and 5000, respectively. HTLV-I has been shown to be associated not only with HAM/TSP but also with T-lymphocytic alveolitis, polymyositis, arthritis, and sicca syndrome. There are also less certain associations with chronic infective dermatitis, Beh et disease, pseudohypoparathyroidism, and systemic lupus erythematosus (Kubota *et al*, 2000).

In this review, the pathological mechanisms of HAM/TSP will be discussed based mainly on the histopathological, immunological, and molecular points of view.

## Histopathologic features of HAM/TSP

Pathological analysis indicates that the disease affects the spinal cord, predominantly at the thoracic level. There is degeneration of the lateral corticospinal tract as well as of the spinocerebellar or spinothalamic tract of the lateral column (Izumo *et al*, 1992). These lesions are associated with perivascular and parenchymal lymphocytic infiltration with the presence of foamy macrophages, proliferation of astrocytes, and fibrillary gliosis (Umehara *et al*, 1993). There is also widespread loss of myelin and axons, particularly in the corticospinal tracts of the spinal cord. Damage is most severe in the middle to lower thoracic regions of the spinal cord. These findings are consistent with a patient's neurological symptoms, such as paraparesis, spasticity, hyperreflexia, and Babinski's sign (Umehara *et al*, 1993).

A nonrandom distribution of affected regions was suggested by an autopsy study that showed that the regions mainly affected are the so-called 'watershed' zones of the spinal cord in patients with HAM/TSP (Izumo *et al*, 1992). Similar findings were also observed in the brain, although to a lesser degree (Moe Moe Aye *et al*, 2000). These results suggest that inflammatory changes occurred simultaneously in the spinal cord and in the brain, with the distribution of inflammed vessels closely correlated with the characteristic vascular architecture of the brain and the spinal cord, which led to a slowing of blood flow.

*1. T-cell subset and cytokine expression*

The patients whose illness were of short duration (2.5 to 4.5 years) showed parenchymal lesions both with marked inflammatory and degenerative changes in both lateral funiculi (henceforth classified as active-chronic lesions), where CD4+ cells, CD8+ cells, and macrophages were evenly distributed (Umehara *et al*, 1993). Immunohistochemistry showed that inflammatory cytokines, including tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-1$\beta$ (IL-1$\beta$), and interferon-$\gamma$ (IFN-$\gamma$) were expressed on perivascular infiltrating macrophages, astrocytes, and microglia (Umehara *et al*, 1994a). In striking contrast, in patients whose duration of illness was from 8 to 10 years, the spinal cord showed monotonous degeneration of both lateral funiculi, with a few inflammatory cells in the subarachnoid and perivascular spaces (henceforth classified as inactive-chronic lesions). In inactive-chronic lesions, predominance of CD8+ cells over CD4+ cells were observed; however, proinflammatory cytokine expressions were down-regulated compared with those of active-chronic lesions. Many hematogenous macrophages were found to be recruited in the active-chronic lesions, and both macrophages and microglias were chronically activated. In addition, monocyte/macrophage recruitment and activation was also down-regulated along with the duration of illness (Abe *et al*, 1999). These studies suggest that immune responses in the spinal cord lesions of HAM/TSP patients gradually change concomitantly with the duration of illness.

*2. CD8+ CTLs infiltrated the CNS of HAM/TSP*

As for the pathogenesis of HAM/TSP, CD8+ cytotoxic T lymphocytes (CTLs) against HTLV-I has been considered as the effecter cells (Jacobson *et al*, 1990). To confirm the role of CD8+ CTLs in the formation of central nervous system (CNS) lesions, the distribution of TIA-1+ cells in the spinal cord lesions of HAM/TSP was analyzed. A novel monoclonal antibody (mAb), designated TIA-1 (Anderson *et al*, 1990), recognizes a 15-kDa granule-associated protein, the expression of which is restricted to CTLs and natural killer (NK) cells. In active-chronic lesions, many TIA-1+ cells are distributed throughout the parenchyma and perivascular cuffs (Umehara *et al*, 1994b). Dual immunolabeling revealed that about 80% of TIA-1+ cells coexpressed the CD8 antigen. In contrast, TIA-1+ cells were scarcely observed in inactive-chronic lesions, though CD8+ cells dominated in the parenchyma and perivascular cuffs. The number of TIA-1+ cells correlated with the amount of HTLV-I proviral DNA in situ. The protein TIA-1 has been associated with the induction of apoptosis in target cells (Tian *et al*, 1991). In active inflammatory lesions, cells undergoing apoptosis were found, most of them being identified as helper-inducer CD45RO+ T lymphocytes (Umehara *et al*, 1994b). These findings suggest that HTLV-I–specific CD8+ CTL-induced apoptosis of CD4+ T lymphocytes may be one of the

possible mechanisms to eliminate HTLV-I–infected cells from the central nervous system.

*3. Fas/FasL expression*

HTLV-I–specific CD8+ CTLs are crucial for viral clearance in HTLV-I infection. In general, CD8+ CTLs exert antiviral effector functions via two basic mechanisms: (1) the exocytosis of perforin-containing granules on cognate target cells; and (2) the engagement of Fas on cognate or neighboring target cells by membrane-bound or released Fas ligand (FasL). Fas/FasL interaction regulates a major pathway in apoptosis, which may play an important role in mediating both the antiviral effects and the inflammatory process in neurological diseases. The level of soluble Fas is increased in the sera of patients with HAM compared with controls (Inoue *et al*, 1997). The levels of soluble FasL are higher either in the sera (Inoue *et al*, 1997) or the CSF (Saito *et al*, 1998) of patients in the active stage of HAM. In addition, FasL mRNA expression is up-regulated in peripheral blood T lymphocytes (Kawahigashi *et al*, 1998). In the spinal cord lesions of HAM/TSP, Fas was preferentially expressed on infiltrating T cells in active chronic lesions (Umehara *et al*, 2002). FasL expression was up-regulated on various cells, mainly microglia/macrophages in active-chronic lesions. These findings suggest that macrophages/microglias may play a key role in the elimination of activated effector T cells in the CNS of HAM/TSP. Therefore, increased FasL expression by macrophages/microglia in active inflammatory lesions of HAM/TSP may represent an immunological response against infiltration of Fas+ T cells in the CNS. In contrast, FasL expression was markedly down-regulated in inactive-chronic lesions of HAM patients who had a long duration of illness. Taken together, these data suggest that the Fas/FasL system may play a role in the down-regulation of the immune reaction in the CNS of HAM/TSP.

*4. Localization of HTLV-I in the CNS of HAM/TSP*

These series of works suggests that HTLV-I–infected CD4+ T lymphocytes enter the CNS, and this drives local expansion of virus specific CD8+ CTLs, which, along with cytokine, causes pathological changes. Therefore, it is important to determine which cells might be targets of CTLs in the CNS. Using semiquantitative polymerase chain reaction (PCR), HTLV-I *pX*, and *pol* sequences were found to be increased in the thoracic cord areas where CD4+ cells predominated (Kubota *et al*, 1994). This proviral load decreased with the increased length of the patient's disease and was paralleled by the number of infiltrating CD4+ cells. By a novel *in situ* PCR technique, HTLV-I DNA was localized to inflammatory UCHL-1–positive cells (Matsuoka *et al*, 1998). Using the same CNS samples, *in situ* hybridization studies have accurately localized HTLV-I tax mRNA to infiltrating CD4+ T lymphocytes in active lesions in CNS specimens from HAM/TSP patients (Moritoyo *et al*, 1996). Taken together, these findings suggest that the main harborer of the HTLV-I virus may be infiltrating CD4+ T lymphocytes, and transcription of the tax gene occurs in some of the HTLV-I–infected CD4+ T lymphocytes.

However, there are some controversial reports that showed that HTLV-I tax mRNA was localized within the neural tissue (some of them were astrocytes), but not in perivascular infiltrates (Lehky *et al*, 1995). The reasons for these differences are unknown, but they may be related to the variations in samples or detection methods.

*5. T cell trafficking into the CNS of HAM/TSP*

Leukocyte adhesion molecules to endothelium plays an important role in the pathogenesis of inflammatory diseases, including HAM/TSP. The spinal cord lesions of HAM/TSP had greater vascular cell adhesion molecule-1 (VCAM-1) expression on endothelium compared with those of controls (Umehara *et al*, 1996). Infiltrating mononuclear cells, especially perivascular lesions, expressed very late antigen-4 (VLA-4). Monocyte chemoattractant protein-1 (MCP-1) was also up-regulated on perivascular infiltrating cells and vascular endothelium in active-chronic inflammatory lesions of HAM/TSP. These findings suggest that VLA-4/VCAM-1 interaction and MCP-1 is involved in mediating T-lymphocyte/macrophage adhesion and chemotaxis in the CNS inflammatory process.

After transendothelial migration, T cells/macrophages then encounter the extracellular matrix (ECM) and must pass through the basement membrane and migrate into the interstitial matrix. Proteolytic disruption of ECM by matrix metalloproteinases (MMPs) is a key process for the damage of the blood-brain barrier (BBB). MMPs have been reported to be involved in inflammatory disorders of the CNS. Immunohistochemical studies revealed that collagen IV and decorin immunoreactivity on the basement membrane of CNS parenchymal vessels was partially disrupted in areas where inflammatory mononuclear cells infiltrated in active-chronic lesions of HAM/TSP (Umehara *et al*, 1998). In these lesions, MMP-2 (gelatinase A) was immunostained mainly on the surface of foamy macrophages and lymphocytes, whereas MMP-9 (gelatinase B) expression was positive in the intravascular and perivascular mononuclear cells but not on foamy macrophages. In contrast, inactive-chronic lesions of the spinal cords of HAM/TSP contained much smaller numbers of MMP-2–positive or MMP-9–positive mononuclear cells than active-chronic lesions. Production levels of MMP-2 and MMP-9 in both sera and CSF were higher in the patients with HAM/TSP than those in noninflammatory other neurological disease controls (ONDs). Using zymography, proMMP-9 was more frequently detected in the CSF of patients with HAM/TSP than those in ONDs (Giraudon *et al*, 1996;

Umehara *et al*, 1998). Taken together, these data indicate that MMP-2 and MMP-9 may play an important role in the BBB breakdown and tissue remodeling in the CNS of HAM/TSP.

*6. Axonal degeneration in spinal cord lesions of HAM/TSP*

Previous neuropathological studies revealed that both myelin destruction and axonal loss are histological hallmarks of actively inflamed lesions of HAM/TSP. Particularly, axonal loss is responsible for the persistent disability characterized by spastic paraparesis and urinary disturbance. The localization and extent of $\beta$-amyloid precursor protein (APP) immunoreactivity as a sensitive marker for impairment of fast axonal transport in the spinal cords of HAM/TSP were investigated. The results from this study show that APP, used as a marker of early axonal damage in HAM/TSP lesions, is more intensively expressed in areas of active inflammatory lesions than those of inactive-chronic lesions (Umehara *et al*, 2000). The close localization to the areas containing inflammation (activation of macrophage/microglia) is striking and suggests that axonal damage is closely associated with inflammation in active-chronic lesions.

## Risk factors for HAM/TSP

The prevalence of HAM/TSP is between 0.1% and 2% of HTLV-I–infected individuals. The lifetime risk of developing this disease among carriers is estimated to be 0.23% in Japan (Kaplan *et al*, 1990). About two-thirds of patients are female (Nakagawa *et al*, 1995). Other known risk factors for HAM/TSP include a high proviral load of HTLV-I (Nagai *et al*, 1998) and a certain HTLV-I subgroup (Furukawa *et al*, 2000). Most people infected with HTLV-I mount a strong CTL response to the virus (Jacobson *et al*, 1990; Bangham, 2000). This strong CTL response protects against the development of HAM/TSP by reducing the proviral load (Jeffery *et al*, 1999). However when the proviral load exceeds a threshold level, HTLV-I–specific CTL could contribute to inflammation (Nagai *et al*, 1998; Jeffery *et al*, 1999). The immune response to HTLV-I is now closer to being understood (Bangham, 2000).

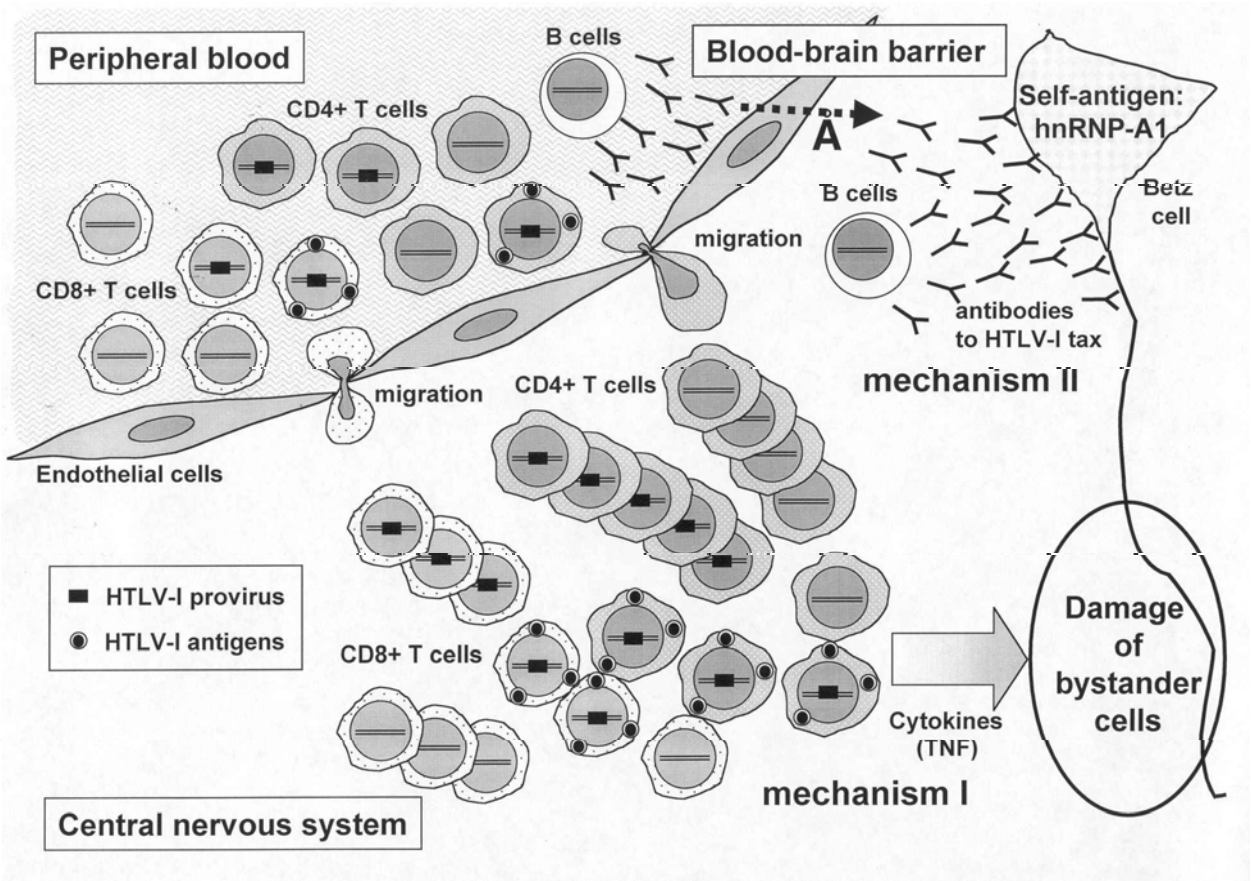


**Figure 1** Pathological mechanisms of developing HAM/TSP. Mechanism I: CD8+ CTL versus target cell (i.e., HTLV-I–infected CD4+ or CD8+ T cells) interaction would produce cytokines including IFN-$\gamma$, which would damage bystander neural tissue. Mechanism II: Immunoglobulin G specific to HTLV-I-tax, which crossreact with heterogeneous nuclear ribonuclear protein-A1 (hnRNP-A1) expressed in Betz cell, would induce damage to the cell.

## Conclusion

Why does HTLV-I cause HAM/TSP in only less than 5% of infected people? To answer this question, many risk factors have been found as mentioned above. The individuals who possess more risk factors may a greater tendency to develop the disease. CD8+ CTL versus target cell (i.e., HTLV-I–infected CD4+ T cells) interaction may play an important role in the CNS inflammatory process in HAM/TSP. Recently, CD8+ cells were also found to be a viral reservoir *in vivo* for HTLV-I in addition to CD4+ cells (Hanon *et al*, 2000; Nagai *et al*, 2001). Therefore the CD8+ T cells in the CNS may also be infected by HTLV-I, although there has been no direct evidence for it. HTLV-I tax will induce up-regulation of various molecules such as adhesion molecules, MMP-9, and inflammatory cytokines (TNF-$\alpha$ IL1-$\beta$, INF-$\gamma$), which result in infiltration of HTLV-I–infected T cells into the CNS. After trafficking into the CNS, HTLV-I–infected T cells exhibit significant viral antigen expression, and the interaction of HTLV-I–infected CD4+ T cells and HTLV-I–specific CD8+ CTLs may lead to secretion of cytokines, MMPs, and FasL in the CNS. In addition, the spontaneous secretion of IFN-$\gamma$ from HTLV-I–infected CD4+ T cells could activate macrophage/microglias, which could also secret IFN-$\gamma$. These cytokines would damage bystander neural tissue (mechanism I, Figure 1).

A recent study supports an additional hypothesis that antibodies would identify a CNS autoantigen in HAM/TSP (Levin *et al*, 2002). Immunoglobulin G isolated from HAM/TSP patients identified heterogeneous nuclear ribonuclear protein-A1 (hnRNP-A1) as the autoantigen. Antibodies to hnRNP-A1 cross-reacted with HTLV-I tax. Immunoglobulin G specifically stained human Betz cells. Infusion of autoantibodies in brain sections inhibited neuronal firing (Levin *et al*, 2002). These data suggest that molecular mimicry between HTLV-I and hnRNP-A1 might be involved in the pathogenesis of HAM/TSP (mechanism II, Figure 1).

Which of these two mechanisms might play a more important role in developing HAM/TSP? The distribution of the affected lesions in the CNS of HAM/TSP (Izumo *et al*, 1992; Moe Moe Aye *et al*, 2000) and the histopathological view described in this review support the more important role of mechanism I. Immunological studies show the important role of T cells (Nagai and Jacobson, 2001), again indicating the importance of mechanism I. HAM/TSP might be caused mainly by mechanism I, and mechanism II might be playing an additional role for developing HAM/TSP (Figure 1).

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